REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the final Office Action mailed February 4, 2009. A Request for Continued Examination along with a petition and the appropriate fee for a three month extension of time has been submitted herewith. In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of the Claims

Claims 70-79 are under consideration in this application. Claims 1-69 stand canceled without prejudice or disclaimer. Claim 70 is amended, as set forth above, to more particularly define and distinctly claim Applicant's invention. All the amendments to the claims are supported by the specification and there is no new matter.

Amendments to the Specification

In response to the Examiner's assertion that the specification does not provide guidance how to correlate data of Tables 5A-5WWW (e.g., GLGC ID Nos.) to the data of Table 1 (SEQ ID NOS.), Applicants have submitted herewith substitute Table 5 (including Tables 5A-5WWW). All of the information contained within substitute Table 5 (including Tables 5A-5WWW) is incorporated by reference herein in this response.

Rejection under 35 USC §112, First Paragraph

Claims 70-79 stand rejected under 35 USC §112, first paragraph, as allegedly not being sufficiently enabled by the specification. Applicants respectfully traverse the rejection.

The Examiner raises the following issues as being allegedly relevant to enabling the present claims:

(1) The specification allegedly does not disclose steps necessary for the comparison of experimental gene expression levels with the claimed hepatotoxicity model to determine whether a test compound is a hepatotoxin;

(2) Tables 5A-5WWW are lengthy and list genes by GLGC ID, and not SEQ ID NO. as in Table 1;

(3) Some genes listed in the Table are allegedly ESTs.

It is noted that the rejection is largely taken verbatim from the final Office Action dated February 5, 2007 in Application Serial No. 10/357,507, now U.S. Patent 7,469,185, which discloses related subject matter and is commonly owned. The Examiner's attention is also respectfully directed to the fact that these rejections were withdrawn in Application Serial No. 10/357,507 on the basis of the claim language already present in this application. While the Applicant understands that the now issued patent was examined by a different examiner, it is believed that, to the extent possible, the standard of enablement should be applied consistently by the Patent Office.

Moreover, the instant specification provides clear guidance that enables a person of ordinary skill in the art to practice the claimed invention without undue experimentation. The specification clearly describes methods of comparing gene expression information, including steps necessary for the comparison of experimental gene expression levels with the claimed hepatotoxicity model to determine whether a test compound is a hepatotoxin. For instance, Example 1 of the instant application provides clear guidance regarding how to identify genes as toxicity markers, including detailed guidance on how to compare gene expression levels between samples in a toxicity group (samples affected by exposure to a toxin) and samples in a non-toxicity group (samples not affected by exposure to a toxin):

> Tables 5A-5WWW disclose a core or alternate set of genes, along with the summary statistics for each of the comparisons performed as indicated in these tables--i.e., expression levels of a particular gene in toxicity group samples compared to non-toxicity group samples in response to exposure to a particular toxin, or as measured in a particular disease state. Each of these tables contains a set of predictive genes and creates a model for predicting the hepatoxicity of an unknown, i.e., untested compound. Each gene is identified by its Gene Logic identification number and can be cross-referenced to a gene name and representative SEQ ID NO. in Table 1 or in one more related applications, as mentioned on page 1. For each comparison of gene expression levels between samples in the toxicity group (samples affected by exposure to a toxin) and samples in the non-toxicity group (samples not affected by exposure to a toxin), the tox mean (for toxicity group samples) is the mean signal intensity, as normalized for the various chip parameters that are being assayed. The non-tox mean represents the mean signal intensity, as normalized for the various chip parameters that are being assayed, in non-toxicity group samples. For individual genes, an increase in the tox mean compared to the non-tox mean indicates up-regulation upon exposure to a toxin, while a decrease in the group mean compared to the non-group mean indicates down-regulation. (paragraph [0193])

The specification provides additional clear guidance regarding methods for normalizing expression intensity to accurately and reliably compare the expression of

individual genes without undue experimentation. For instance, the specification describes the following exemplary methods for normalization of expression values:

> The mean values are derived from Average Difference (AveDiff) values for a particular gene, averaged across the corresponding samples. Each individual Average Difference value is calculated by integrating the intensity information from multiple probe pairs that are tiled for a particular fragment. The normalization multiplies each expression intensity for a given experiment (chip) by a global scaling factor. The intent of this normalization is to make comparisons of individual genes between chips possible. The scaling factor is calculated as follows: 1. From all the unnormalized expression values in the experiment, delete the largest 2% and smallest 2% of the values. That is, if the experiment yields 10,000 expression values, order the values and delete the smallest 200 and largest 200. 2. Compute the trimmed mean, which is equal to the mean of the remaining values. 3. Compute the scale factor SF=100/(trimmed mean). (*see* paragraphs [0194]-[0197])

The specification provides further detailed guidance regarding steps necessary for the comparison of experimental gene expression levels with the claimed hepatotoxicity model to determine whether a test compound is a hepatotoxin. For instance, Example 2 describes exemplary methods for toxicity modeling, including linear discriminant models for evaluating toxic and non-toxic samples, and the use of Principal Components Analysis (PCA) for toxicity modeling. Moreover, Example 3 describes methods in which gene expression profiles prepared from expression data, in the presence and absence of toxin treatment, can be used as controls in assays of compounds whose toxic properties have not been examined. The specification provides further guidance on modeling methods that accurately and reliably predict whether a test compound is a hepatotoxin based on comparison of gene expression profiles to a hepatotoxicity model, as instantly claimed.

With respect to the Examiner's distinction between genes and ESTs, it is the Applicant's position that such does not impact the enablement of the claimed methods. Indeed, this rejection was ultimately withdrawn in Application Serial No. 10/357,507 without amendment on the part of the Applicant.

With regards to the Examiner's assertion that Tables 5A-5WWW are lengthy and list genes by GLGC ID, and not SEQ ID NO. as in Table 1, Applicants have submitted a an amended Table 5 herewith, which provides corresponding SEQ ID NOS.

Therefore, in view of the clear guidance in the specification and the numerous working examples provided by Applicants, it would not require undue experimentation to practice the claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 USC §112, Second Paragraph

Claims 70-79 stand rejected under 35 USC §112, second paragraph, as allegedly being indefinite.

The Examiner asserts that the language "differential gene expression levels for said at least ten genes upon exposure to the test compound" is unclear. This ground for rejection is respectfully traversed because the language of claim 70 is sufficiently clear on its face. The language "differential gene expression levels for said at least ten genes upon exposure to the test compound" clearly indicates that the test compound is inducing the "differential" gene expression (e.g., as opposed to when the test compound is not present).

To more particularly define and distinctly claim Applicant's invention, claim 70 has been amended to address the Examiner's assertion regarding lack of antecedent basis for "the" normalized mean expression levels.

Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Provisional Obviousness-Type Double Patenting Rejections

Claims 70-79 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over one or more claims of Application Serial Nos. 11/059,535; 10/515,373; 11/547,759; 12/043,666; 12/181,020; and 12/256,225.

In response, Applicants filed a terminal disclaimer on June 4, 2009, with respect to Application Serial No. 11/059,535. According to the latest records on Public PAIR, this terminal disclaimer has been approved by the U.S. Patent Office. According to the Examiner's statements in the Advisory Action mailed on June 29, 2009, the terminal disclaimer if entered would be sufficient to overcome the provisional obviousness-type double patenting rejection.

As for the remaining provisional obviousness-type double patenting rejections, the Examiner's attention is respectfully directed to MPEP §804(I)(B):

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Thus, upon withdrawal of the Section 112 rejections (which is respectfully requested), the provisional obviousness-type double patenting rejections over application numbers 10/515,373; 11/547,759; 12/043,666; 12/181,020; and 12/256,225 should also be withdrawn.

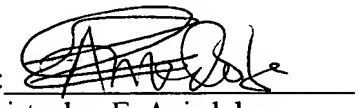
Conclusion

In view of all the above, favorable reconsideration of this application is respectfully requested. Should there be any outstanding issues requiring discussion that would further the prosecution and allowance of the above-captioned application, the Examiner is invited to contact the Applicant's undersigned representative at the address and phone number indicated below.

It is asserted that this response is timely and that additional fees, beyond those that may otherwise be provided for in accompanying documents, are not required. However, in the event that additional fees are necessary to prevent abandonment of this application, then such fees required therefor are hereby authorized to be charged to our Deposit Account No. 50-4336. The Commissioner is also requested to credit any overpayment to Deposit Account No. 50-4336.

Respectfully submitted,

DOBE LAW GROUP, LLC

By: 
Christopher E. Aniedobe
Reg. No. 48,293

Date: August 04, 2009

Dobe Law Group, LLC
7207 Hanover Parkway
Suite C/D
Greenbelt, MD 20770
Phone: 301 982 0154
Fax: 301 982 0154
Email: Chris@DobeLawGroup.com